The influence of uterine function on embryonic and fetal survival[1]

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ABSTRACT: The secretion rate of growth factors and the delivery rate of nutrients by the uterus to the conceptus affects the growth rate, development, and survival of the conceptus. For most growth factors and nutrients, passage into the uterus is not simply controlled by diffusion. Many growth factors are products of uterine tissue. Transport of some nutrients is aided by specific transporter molecules on the uterine endometrial epithelial cell, whereas others (e.g., retinol, iron, and folate) are incorporated into uterine-secreted proteins (e.g., retinol binding protein, uteroferrin, and folate binding protein). The rate of production of these proteins during pregnancy profoundly affects pregnancy outcome. Uterine gland knockout experiments in sheep demonstrate that pregnancy fails in the absence of uterine glands, the source of many uterine-secreted proteins. In pigs, both global and specific effects of uterine products on aspects of conceptus development can influence litter size. The provision of growth factors and nutrients by the uterus plays a role in entraining conceptus development, so that the uterine environment and the developmental stage of the conceptus match. This uterine-dependent control of conceptus development influences pregnancy success. For example, the uterus of the Meishan pig secretes less protein prior to elongation, which slows conceptus development, results in smaller placentas and smaller fetuses, and allows for greater litter size. Furthermore, in Occidental pig breeds, an earlier rise in progesterone at the beginning of pregnancy accelerates the onset of protein secretion, increases estrogen secretion by the conceptus, increases the size of the fetus in later pregnancy, and decreases litter size. Studies of fetal erythropoiesis also indicate that specific uterine products (uteroferrin and folate binding protein) are required for this important aspect of fetal development and that greater litter size is associated with improved erythropoiesis. Thus, manipulation of uterine function can modify conceptus development and affect pregnancy success in domestic livestock.

Key Words: Embryo, Fetus, Mortality, Perinatal, Progesterone, Stillbirth

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Introduction

Studies indicate that the rate of conceptus loss in domestic livestock during early pregnancy (i.e., embryonic mortality occurring before implantation) ranges from 20 to 40% (Hanly, 1961; Perry and Rowlands, 1962). When attempts are made to increase the number of conceptuses in the uterus of pigs (Day et al., 1967; Bazer et al., 1969; Vallet, 2000), further losses occur during later gestation, primarily due to the effects of intrauterine crowding. This same phenomenon also occurs in cattle as the number of conceptuses in utero is increased to triplets (Echternkamp, 1992). Losses resulting from intrauterine crowding in swine are due to limitations in uterine capacity, which has been functionally defined as the number of conceptuses that can be maintained by the uterus until term (Christenson et al., 1987). In the past, fully formed fetuses, whether alive or stillborn, were included when estimating uterine capacity (Christenson et al., 1987; Christenson and Leymaster, 2000). Thus, a final component of conceptus loss during gestation is the incidence of stillbirths. Stillbirths occur at a rate of around 5 to 10% in domestic livestock (Christianson, 1992; Nix et al., 1998; Meyer et al., 2000).

Background

Although embryonic mortality occurs naturally, it can be induced using a variety of treatments, which have led to improvements in our understanding of this process. Conceptus-uterine asynchrony will cause embryonic loss (Rowson and Moor, 1966; Newcomb and Rowson, 1975; Polge, 1982). Some nutritional manipulations also increase embryonic loss (Foxcroft, 1997).

[1]Names are necessary to report factually on available data; however, the USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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Furthermore, in ruminants, embryonic loss occurs when the progesterone corresponding to a previous cycle or the estrogen corresponding to estrus is omitted (Miller and Moore, 1976a). Several factors also influence mortality caused by limitations in uterine capacity. In the Meishan pig, increased uterine capacity is associated with slower conceptus growth during early pregnancy (Ford and Youngs, 1993) and later pregnancy (Christenson, 1993; Wilson et al., 1998). The efficiency of fetal erythropoiesis may also influence uterine capacity (Vallet, 2000). Finally, it has been shown that the risk of stillbirth is negatively correlated with piglet weight at birth (Christianson, 1992). Small piglets are at greatest risk of loss during parturition, again suggesting that conceptus growth rate during pregnancy influences conceptus loss. Unfortunately, effects of fetal/piglet weight on uterine capacity and the incidence of stillbirth appear to oppose each other, and litter size may be the result of a compromise between these two mechanisms. In sheep and cattle, large offspring are associated with increased dystocia and stillbirths (Nix et al., 1998; Meyer et al., 2000). Various components of uterine function contribute to each of these mechanisms. However, it is not yet clear how uterine function is controlled during various stages of pregnancy and what may be done to improve conceptus survival during early pregnancy, midgestation, and the perinatal period.

Embryonic Mortality

The detrimental effect of asynchrony between the embryo and the uterine environment on embryo survival has been shown through the use of embryo transfer experiments in each domestic livestock species (Rowson and Moor, 1966; Newcomb and Rowson, 1975; Wilmut et al., 1985). For all domestic livestock, these experiments indicated that asynchrony between the embryo donor and the recipient results in failure of pregnancy. In general, embryonic loss due to asynchrony is less when embryo development is advanced compared to uterine stage (Polge, 1982). In addition, the effect of the naturally occurring variation in embryo development on embryo mortality in pigs has been convincingly demonstrated (Pope, 1990). Embryos resulting from ova that ovulate last are the ones most likely to be lost. If these embryos from late-ovulating ova are transferred into a recipient that was in estrus 1 d later than the donor of the embryos, the embryos develop appropriately. In ruminants, because multiple ovulations are less common, variation in synchrony between the embryo and the uterus and any effect it might have on embryo survival is more difficult to demonstrate. However, asynchronous embryo transfer suggests at least the possibility that asynchrony between the embryo and uterine environment may be responsible for embryonic loss in ruminants. Thus, components of uterine function must be responsible for the embryo loss due to asynchrony.

Nutritional manipulation also increases embryonic loss (Foxcroft, 1997). Increased feeding just prior to estrus results in an increase in ovulation rate, but it also increases embryo mortality (Ashworth et al., 1989; Ashworth, 1991). Other studies indicate that restricted feeding followed by unrestricted feeding near the time of expected estrus also increases embryo mortality (Jindal et al., 1997; Almeida et al., 2000). These effects have been associated with decreased progesterone secretion during early pregnancy (Ashworth et al., 1989; Jindal et al., 1996, 1997; Almeida et al., 2000). However, the effect of exogenous progesterone during early pregnancy on embryo survival depends on the nutritional model used (Ashworth, 1991; Jindal et al., 1997; Mao and Foxcroft, 1998), sometimes increasing and sometimes decreasing embryonic mortality. Nevertheless, the timing of the increase in progesterone influences the function of both the uterus and the embryo (see below), supporting the possibility that some of the nutritional effects on embryo mortality are due to progesterone-controlled changes in uterine function.

Embryo mortality also occurs in ovariectomized ewes unless progesterone corresponding to a previous cycle and estrogen corresponding to estrus is included in the steroid replacement regimen (Miller and Moore, 1976; Miller et al., 1977). These results indicate that the correct endocrine sequence is required in sheep to prepare the uterus for pregnancy, again suggesting a potential role for the uterus in embryo losses. However, this requirement does not appear to be present in pigs, because the first cycle after weaning in pigs is fertile despite the lack of progesterone.

Components of uterine function responsible for embryonic mortality resulting from asynchrony, nutrition or improper endocrine patterns are not fully understood. However, the uterus plays a key role in maternal recognition of pregnancy, embryo elongation, implantation, and support of the developing embryo during this period of early pregnancy. Faults in any of these mechanisms could be responsible for embryonic mortality.

Maternal recognition of pregnancy in pigs (d 11) has been well studied. Corpus luteum (**CL**) regression is caused by uterine prostaglandin (PG) F_{2a} secretion into the uterine venous drainage (Moeljono et al., 1976). The release of PGF_{2a} into the uterine venous drainage is abrogated in pregnancy (Moeljono et al., 1977). The effect of the embryo on PGF_{2a} release is caused by embryonic estrogen secretion (Frank et al., 1977, 1978; Marengo et al., 1986). It has been suggested that embryonic estrogen accomplishes this by redirecting PGF_{2a} secretion into the uterine lumen and away from the uterine vascular drainage (Bazer and Thatcher, 1977; Bazer et al., 1984), a hypothesis that has not been convincingly disproved to date. However, recent results from several laboratories suggest that many components involved in CL regression in ruminants, most notably oxytocin and oxytocin receptors (see below), are also present in the pig. Treatment of pigs with oxytocin stimulates PGF_{2a} secretion by the uterus (Carnahan et

al., 1996). However, the CL is not the source of oxytocin in pigs. Instead, oxytocin appears to be secreted by the endometrium (Trout et al., 1995; Boulton et al., 1996; Vallet et al., 1998b). Oxytocin receptors are also present on endometrium (Whiteaker et al., 1994; Okano et al., 1996). Oxytocin secretion by the uterus has been shown to be greater during pregnancy than during the estrous cycle (Trout et al., 1995; Vallet et al., 1998b), although a significant amount of oxytocin was found in the uterine lumen of cyclic gilts (Vallet et al., 1998b). Thus, the role in luteolysis and maternal recognition of pregnancy of endometrial secretion of oxytocin, endometrial oxytocin receptors, the ability of oxytocin to cause the release of endometrial PGF_{2a}, and the increase in oxytocin secretion by the endometrium during pregnancy remains unclear. Possibly, luteolysis is controlled by the intermittent paracrine release of oxytocin by endometrial cells. During pregnancy, the endometrium may either release more oxytocin or have a more sustained release of oxytocin, causing down-regulation of oxytocin receptors or redirection of PGF_{2a}. Furthermore, oxytocin may interact with estrogen in some as-yet-unknown way to redirect PGF_{2a} secretion into the uterine lumen. The importance of endometrial oxytocin in luteolysis and its interaction with embryonic estrogen secretion regarding maternal recognition of pregnancy warrants further study. Also, because the release of oxytocin by the endometrium during pregnancy is likely to alter the intrauterine environment, the contribution of endometrial oxytocin to embryonic loss should be investigated.

Maternal recognition of pregnancy in sheep and cattle (d 13 and 16, respectively), has also been well-studied. As in pigs, luteolysis is caused by PGF_{2a} release from the uterus (Chamley et al., 1972; Cerini et al., 1973). The role of oxytocin and oxytocin receptors in this process has been clearly established. The source of oxytocin appears to be both the neurohypophysis and the CL (Flint et al., 1990) and oxytocin causes release of PGF_{2a} from the uterus. Progesterone treatment early in the estrous cycle advances the onset of luteolysis in sheep (Ottobre et al., 1980) and cattle (Garrett et al., 1988a) and functional oxytocin receptors are expressed on endometrial cells in sheep after approximately 10 d of continuous progesterone treatment (Vallet et al., 1990; Vallet and Lamming, 1991). These findings indicate the role of progesterone timing in the control of luteolysis in ruminants. There is also evidence that progesterone in the previous cycle and estrogen secreted during estrus can affect the timing of the onset of the luteolytic mechanism, suggesting a reason for the influence of the correct endocrine pattern on embryo mortality (Vallet et al., 1990). To inhibit luteolysis, ruminant embryos secrete interferon-tau (Imakawa et al., 1987; Stewart et al., 1987), which blocks the induction of functional oxytocin receptors (Vallet and Lamming, 1991; Lamming et al., 1991; Robinson et al., 1999). This effect may occur due to inhibition of the induction of estrogen receptor by interferon-tau (Spencer and Bazer, 1996), possibly by stabilization of the negative effect of progesterone on the luteolytic mechanism, because progesterone is required for the effect of interferon (Vallet and Bazer, 1989; Vallet and Lamming, 1991). However, this does not occur by rescue of endometrial progesterone receptors, because progesterone receptors disappear from endometrial epithelial cells in both pregnant and nonpregnant ewes (Ott et al., 1993). How the effect of progesterone is maintained without progesterone receptors is not known but is most likely the result of an interaction between the uterine stroma, which does continue to have progesterone receptors, and the endometrial epithelium, which does not.

In sheep and cattle, other changes in endometrial function also occur during pregnancy, and these changes are likely to be involved in embryo elongation, implantation, or embryo support. Interferon-tau alters the secretion of several endometrial proteins (Godkin et al., 1984; Vallet et al., 1987; Sharif et al., 1989). Progesterone treatments during the first few days of the estrous cycle also alters uterine protein secretion, suggesting a role for progesterone timing in this process as well as luteolysis (Garrett et al., 1988b; Ashworth and Bazer, 1989). With few exceptions (Vallet et al., 1991; Austin et al., 1996; Johnson et al., 1999), the identity and function of these proteins are not known. Nevertheless, they are likely to be essential for continued embryo survival, because neonatal progestogen treatment, which inhibits the formation of the uterine glands in neonatal lambs, blocks the establishment of pregnancy in subsequent adulthood (Gray et al., 2000). Furthermore, early progesterone treatment of sheep (Lawson and Cahill, 1983) and cattle (Geisert et al., 1991) allows for the successful transfer of more advanced embryos into the uterus.

Changes in the secretion of proteins by the uterus also occur during the time of maternal recognition of pregnancy in pigs. Some of these proteins have either clearly defined or hypothetical functions during pregnancy. Uteroferrin (Roberts and Bazer, 1988), retinol binding protein (Roberts et al., 1993), and folate binding protein (Vallet et al., 1998a) deliver iron, retinol, and folate to the developing embryo. Numerous growth factors are also secreted (Geisert and Yelich, 1997; Simmen et al., 1991; Wilson et al., 1997). For many years it was hypothesized that the changes in uterine protein secretion during this period occurred in response to embryonic estrogen (Geisert et al., 1982b), paralleling the effects of interferon on uterine protein secretion in ruminants. However, in swine as in ruminants, recent evidence suggests that secretion of many endometrial proteins is unlikely to be controlled solely by the embryo. Some proteins are influenced by the embryo, whereas others are controlled by continued progesterone support, presumably by a mechanism similar to that controlling protein secretion and luteolysis in ruminants. We (Vallet et al., 1998b) recently compared the uterine secretion of uteroferrin, retinol binding protein, folate binding protein, oxytocin, and total protein

from d 10 to 15 of the estrous cycle and pregnancy in untreated and progesterone-treated gilts (d 2 and 3 of the cycle or pregnancy). The early progesterone treatment accelerated the changes in secretion of total protein, uteroferrin, retinol binding protein, and folate binding protein but did not affect oxytocin secretion. Only uteroferrin and oxytocin were altered in the presence of the embryo. Thus, total protein, uteroferrin, retinol binding protein, and folate binding protein represent uterine products that are controlled substantially by continued progesterone support. The effect of progesterone timing could thus mediate the effect of nutrition on progesterone secretion and embryo mortality during early pregnancy. Only uteroferrin and oxytocin were influenced by the presence of the embryo. It is, therefore, likely that many uterine-secreted proteins, and probably other uterine factors such as ions and prostaglandins, also differ in whether they are controlled by progesterone timing, the presence of the embryo, or both. Because these changes dramatically alter the intrauterine environment, possibly creating a hostile environment for slower-developing embryos, determination of the control of these changes is essential in understanding mechanisms of embryo loss.

Another major milestone in embryo development during this period that can influence embryo survival is elongation. Sheep, cattle, and swine embryos all undergo a transition from a spherical embryo to filamentous embryo at around the time of maternal recognition of pregnancy. This process is clearly uterine-dependent, because embryo elongation has never been accomplished in vitro. Control of this process is close to a complete mystery. The onset of elongation appears to correspond with the developmental stage of mesodermal outgrowth within the embryo (Stroband and Van Der Lende, 1990), but details regarding uterine factors that may initiate and(or) support elongation are lacking. One can speculate that elongation must involve some interaction between the surface of the embryo and the endometrial luminal epithelium, but the details of this interaction are not known. Nevertheless, evidence suggests that variation in elongation may influence embryonic survival in swine. Embryo survival is known to be greater in the Meishan pig (Galvin et al., 1993). It has been shown that embryo development occurs slower in the Meishan (Anderson et al., 1993), and that this is a uterine-dependent phenomenon (Youngs et al., 1994). Reciprocal embryo transfer studies indicate that development of both Occidental and Meishan embryos occurs more slowly in the uterine environment of Meishan gilts than in the uterine environment of Occidental gilts (Ford and Youngs, 1993), although there was also an effect of genotype of the embryo as well. However, embryos in the uterine environment of Meishan gilts elongate at the same time as those in the uterine environment of Occidental gilts (Rivera et al., 1996), despite their smaller size, confirming that elongation is not necessarily controlled by the size of the embryo (Ford and Youngs, 1993). The uterine environment of the Meishan also causes the embryos to secrete less estrogen (Ford and Youngs, 1993; Kaminski et al., 1997; Vallet et al., 1998b). However, it remains unclear whether differences in elongation and(or) estrogen secretion play a role in embryo survival.

Despite the fact that the smaller Meishan embryos and larger Occidental embryos elongate at the same time in the Meishan uterine environment, within a litter, more advanced pig embryos clearly elongate earlier than their slower-developing littermates, because embryos in various stages of elongation are observed on d 11 to 12 of pregnancy (Geisert et al., 1982a; Pope et al., 1990). The extent of embryo elongation of more advanced embryos can negatively affect slower-developing littermates because embryos do not appear to elongate past each other even under crowded intrauterine conditions. Thus, elongation appears to cease when the ends of the elongating embryos approach each other. Because of this, one possible mechanism for embryonic loss may be that the early-elongating embryos take up and(or) modify the uterine surface, effectively preventing the elongation of less-advanced embryos. This potentially leaves the slower-developing embryo with insufficient access to the uterine surface and it may be lost for this reason. Thus, elongation to a smaller length, as occurs in the Meishan, could improve survival of the whole litter by decreasing competition for space. How one embryo alters the uterine surface to prevent the continued elongation of its littermate is not known, but results suggest that this is unlikely to be due to embryonic estrogen secretion on the uterus. Estrogen treatment given to pregnant gilts before the normal time of maternal recognition of pregnancy disrupts pregnancy (Morgan et al., 1987a,b) but does not inhibit embryo elongation, and instead the embryos degenerate some time after elongation (Geisert et al., 1991). This degeneration of the embryos occurs coincidently with changes in the endometrial surface epithelium and in uterine protein secretion, suggesting that early estrogen treatment may block implantation or interfere with the nutritional support of the embryo (Gries et al., 1989; Blair et al., 1991). This result suggests that early estrogen treatment influences uterine mechanisms other than elongation that can have a negative impact on the embryo. However, it is still unclear whether embryonic loss in the early estrogen-treated model results in physiological changes in the uterine environment. Nevertheless, these data suggest that both embryo elongation and embryonic estrogen secretion represent potentially separate mechanisms that influence embryonic survival.

Meishan pigs appear to increase embryonic survival by reducing the growth rate and estrogen production of the embryo and, as previously indicated, this is a uterine-dependent phenomenon. Examination of uterine function during the period surrounding embryo elongation indicates that the secretion of many uterine proteins is reduced in Meishans, including IGF-I (Wilson et al., 1997), total protein, uteroferrin, and retinol

binding protein (Ford and Youngs, 1993; Vallet et al., 1998). In contrast, other proteins, such as secreted folate binding protein, are similar between the Meishan and white crossbred pigs (Vallet et al., 1999a). Lower production of some uterine proteins by the Meishan gilt is likely responsible for the slower growth and lower estrogen production by the embryo, but because the secretion of many proteins is decreased in the Meishan during this period, identification of those factors responsible will be difficult. It has also been reported that treating Meishan pigs with exogenous estrogen during this period increases placental weights during later pregnancy (Wilson and Ford, 2001), suggesting that lower embryonic estrogen secretion in the Meishan pig may reinforce the decrease in uterine protein secretion for some proteins. However, it is not yet clear which proteins are influenced by embryonic estrogen, nor is it clear which proteins influence embryonic growth and development.

Uterine Capacity

Changes in embryonic development in response to the uterine environment during early pregnancy have another consequence in addition to modifying the risk of embryonic loss during the time of maternal recognition of pregnancy. This is because the extent of elongation of the embryo during the time of maternal recognition of pregnancy influences the subsequent size of the placenta, and, in turn, the subsequent growth of the fetus. The sizes of the placenta and fetus affect both the space taken up by the developing conceptus within the uterus and the amount of nutrients required to maintain the fetus and placenta during the rest of gestation. In support of this concept, Meishan pigs have smaller placentas and fetuses during later gestation (Christenson, 1993; Biensen et al., 1998), and it is likely that this effect contributes to increased uterine capacity in this breed. In addition, selection of pigs resulting in a reduction in the size of the placenta increased litter size (Wilson et al., 1999). Furthermore, in a recent experiment that examined factors contributing to uterine capacity in a group of half-Meishan, half-White crossbred gilts, fetal weights, even after adjusting for placental weight, which should remove much of the influence of litter size on fetal weights, remained negatively correlated with uterine capacity (Figure 1). Although this correlation cannot be used to assign cause and effect, it confirms that large fetuses are associated with lower uterine capacity (Vallet et al., 2002). This negative association has been further demonstrated using early progesterone treatment of unilaterally hysterectomized-ovariectomized (**UHO**) gilts. As previously indicated, early progesterone treatment has been shown to accelerate both the onset of uterine protein secretion and embryonic estrogen secretion in pigs (Vallet et al., 1998b). Early progesterone treatment decreased litter size in UHO gilts (an experimental model used to estimate uterine capacity) and increased fetal weight but

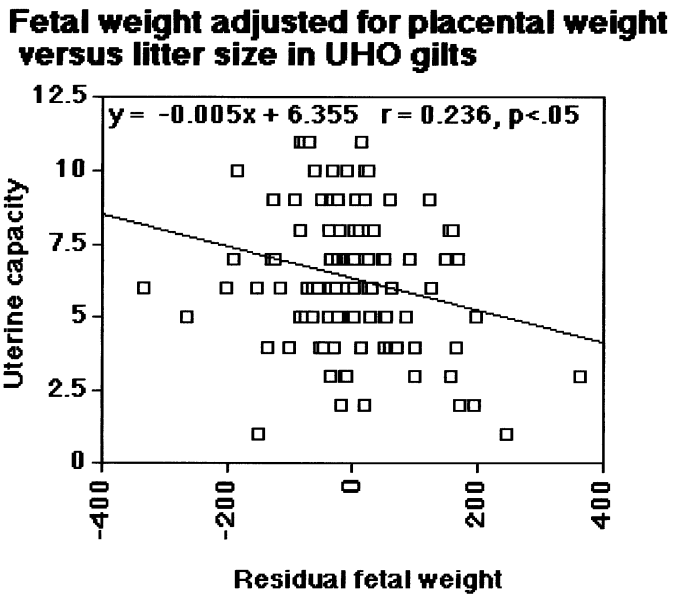

Figure 1. A scatterplot of the relationship between uterine capacity and residual fetal weight is illustrated. Residual fetal weight was obtained by adjusting fetal weight for placental weight and the square of placental weight using regression.

did not change placental weight (Table 1). One possible explanation for these results is that fetal growth is accelerated by early progesterone treatment, which has also been observed in ruminants (Kleemann et al., 1994; 2001). This faster growth rate may put greater demand on delivery of nutrients by the placenta, and may put conceptuses at greater risk for loss. Although it is possible that early progesterone treatment may also have reduced litter size by interfering with either fertilization or early embryonic mortality, half the difference in litter size between the control and progesterone-treated gilts was accounted for by the difference in the number

Table 1. Least squares means for uterine capacity, number of mummies, placental and fetal weights, and placental efficiency (fetal weight/placental weight) for unilaterally hysterectomized gilts treated with either no treatment (control), estradiol treatment (5 mg estradiol valerate given on d 11 and 12 of gestation), or progesterone treatment (200 mg/d on d 2 and 3 of gestation) and then slaughtered on d 105 of gestation

Trait	Control	Estradiol	Progesterone
Uterine capacity[a]	6.9 ± 0.5	6.2 ± 0.6	5.6 ± 0.4
Number of mummies	0.8 ± 0.3	0.7 ± 0.4	1.4 ± 0.3
Placental weight	203 ± 10.6	197.6 ± 12.6	201.3 ± 9.8
Fetal weight[b]	848 ± 21	840 ± 25	926 ± 19
Placental efficiency[c]	4.28 ± 0.11	4.28 ± 0.14	4.64 ± 0.11

[a]Control vs progesterone treatment ($P = 0.05$).
[b]Control vs progesterone treatment ($P = 0.01$) after correction for placental weight.
[c]Control vs progesterone treatment ($P < 0.05$).

of mummified fetuses between the two groups (Table 1). These results suggest that at least a portion of the losses associated with early progesterone treatment occurred during later pregnancy, not during the time of fertilization or embryonic development. Taken together, these results indicate that placental and fetal growth rates influence uterine capacity, and that changes in uterine function in response to early progesterone treatment is one component influencing these growth rates.

Evidence from progesterone-treated gilts and from Meishan gilts suggests that uterine function can affect fetal weight, but how much of the normal variation in fetal/piglet birth weight can be attributed to variation in uterine function? A partial answer to this question can be obtained by dividing the variation in fetal/piglet weights into those portions corresponding to fetal direct genetic effects, maternal genetic effects, and maternal environmental effects. The proportion of the variance in d-105 fetal weights due to direct genetic effects of the fetus (i.e., heritability) was 0.05 ± 0.07 (Vallet et al., 2001). The proportion of the variance in neonatal birth weight due to piglet direct genetic effects was estimated at 0.02 and 0.06 in two different populations of pigs (Cassady et al., 2002). In this latter analysis, the proportion of the variance in birth weights due to maternal genetic effects was 0.09 and 0.29 for the same populations. The proportion of the variance due to maternal random environmental effects, nongenetic in nature, was 0.22 and 0.17 for the same populations. Thus, direct genetic effects of the fetus account for a small proportion of the variation in piglet weight, and thus by inference the variation in fetal growth and development. Combining the maternal genetic and maternal environmental variance components of piglet birth weight indicates that from 30 to 46% of the variation in birth weight is due to the sow, 7- to 14-fold more than that attributable to the genotype of the piglet. Unfortunately, it is not possible to conclude from this analysis what components of the maternal environment are responsible for the variation in piglet weight, but it seems likely from the previous discussion that a portion is due to uterine function.

The fact that early progesterone treatment of sheep, cattle, and swine accelerates both uterine function and embryo development indicates the central role of progesterone in timing changes in uterine function during early pregnancy, and the influence of those changes on embryo development. Evidence that the presence of progesterone continues to effect the timing of changes in uterine function during later pregnancy also exists in both pigs and sheep. Progesterone treatment of ovariectomized pigs for 60 d induces uteroferrin secretion to levels qualitatively similar to those in pregnant pigs (Roberts et al., 1987). In sheep, similar long-term treatment of ovariectomized sheep with progesterone induces the secretion of the uterine milk proteins (Ing et al., 1989), again to levels qualitatively similar to those occurring during midpregnancy. How progesterone

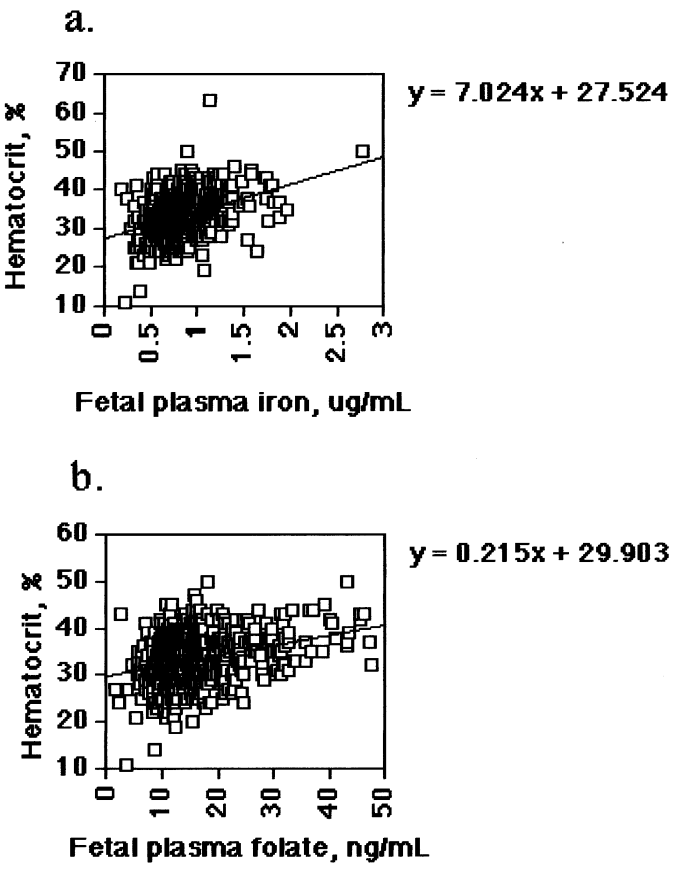

Figure 2. Scatterplots of the relationship between hematocrit and fetal plasma iron (a) and fetal plasma folate (b) in unilaterally hysterectomized-ovariectomized gilts are illustrated.

times both early (i.e., those at the time of maternal recognition of pregnancy) and late (i.e., those occurring after implantation and placentation) events is not fully understood. Paradoxically, as previously indicated in sheep, in both sheep (Ott et al., 1993) and swine (Geisert et al., 1994) endometrial epithelial progesterone receptors disappear during early pregnancy, coincident with the major changes in uterine function associated with the onset of luteolysis and uterine protein secretion. Furthermore, endometrial epithelial cells lack progesterone receptors apparently for the remainder of pregnancy. In spite of this, progesterone treatment somehow induces later increases in uteroferrin and the uterine milk proteins in pigs and sheep, respectively. Progesterone may continue to control these events via paracrine effects of stromal cells, which do maintain progesterone receptors.

Aside from effects on overall fetal and placental growth rates, there are other aspects of uterine function that may influence the health and survival of the fetus. By providing nutrients to the conceptus, the uterus influences the development of specific organ systems that are necessary for fetal survival. One fetal system necessary for survival and requiring input from the uterus is the development of the fetal blood supply.

Table 2. Least squares means for traits measured on d 35 of pregnancy in White crossbred (WC) and Meishan (ME) gilts

Traits	WC	ME
CL	14.4 ± 0.6	15.1 ± 0.6
Litter size	11.4 ± 0.6	12.7 ± 0.7
Placental weight, g	32.7 ± 1.8	21.5 ± 2.0**
Fetal weight, g	3.7 ± 0.1	3.1 ± 0.2**
Hematocrit, %	20.3 ± 0.8	21.2 ± 0.9
Hemoglobin, g/dL	5.2 ± 0.2	4.2 ± 0.2**
Red blood cells, $\times 10^6$/mL	1.08 ± 0.08	1.71 ± 0.09**
Nucleated blood cells, %	29.5 ± 2.2	17.2 ± 2.4**
Reticulocytes, %	45.1 ± 1.7	32.9 ± 1.8**

**Mean was different from WC-INT group ($P < 0.01$).

Both iron and folate are required for erythropoiesis (Bowering et al., 1980; Rodriguez, 1980). As previously indicated, these compounds are provided to the developing conceptus in the form of uteroferrin and secreted folate binding protein, respectively. Thus, the amount of uteroferrin and folate binding protein available to the conceptus is likely to have an influence on the efficiency of this process. In support of this, intrauterine crowding increased the incidence of underweight fetuses, and fetal hematocrits, fetal plasma iron, and fetal plasma folate concentrations are all lower in these fetuses (Figure 2). Also, selection for uterine capacity for 11 generations raised uterine capacity by about one pig per uterine horn and resulted in higher hematocrits in fetuses at 105 d of gestation (Vallet et al., 2001), again suggesting that the two may be associated. Finally, it has also been shown that fetal erythropoiesis during early pregnancy is accelerated in Meishan pigs, possibly contributing to the greater uterine capacity in this breed (Pearson et al., 1998; Table 2). Taken together, these results are consistent with the hypothesis that the impairment of fetal blood development under crowded intrauterine conditions may contribute to fetal losses due to uterine capacity. It also suggests that improved secretion of uteroferrin and folate binding protein by the pig uterus may be one way to improve fetal erythropoiesis, in turn influencing the health and survival of fetuses in crowded intrauterine conditions.

Uteroferrin secretion by the uterus increases 20-fold from d 20 to 40 of pregnancy, coincident with the maturation of the fetal blood supply (Vallet et al., 1996; Pearson et al., 1998). As previously indicated, uteroferrin secretion is largely controlled by continued progesterone support. However, a comparison between pregnant and pseudopregnant pigs indicated that uteroferrin secretion in pregnant pigs is approximately double the rate in pseudopregnant pigs, indicating that the conceptus also modulates uteroferrin secretion during later pregnancy (Vallet and Christenson, 1996). This may or may not be due to placental estrogens, because estrogen stimulated uteroferrin secretion in pseudopregnant pigs, but not in pregnant pigs (Vallet and Christenson, 1996). A recent report suggested that an unidentified low molecular weight factor from the conceptus may be responsible for the effect of the conceptus on protein secretion (Reed et al., 1998). Thus, methods that can alter uteroferrin secretion during midpregnancy are not currently available. Clues to possible methods to modify uteroferrin secretion await further studies defining how the dramatic changes in uteroferrin during pregnancy are controlled by progesterone and the conceptus.

Even less is known about the control of folate binding protein during midpregnancy. Uterine secretion of folate binding protein has only been characterized up to d 15 of the estrous cycle and pregnancy. Unfortunately,

Table 3. The number, percentage stillborn, and relative risk (relative to overall risk) of stillbirths in weight classes of neonatal pigs born to gilts from lines selected either at random (CO) or for ovulation rate (OR) or uterine capacity (UC)

Treatment/trait	≤0.45 kg	0.49 to 0.9 kg	0.95 to 1.36 kg	1.41 to 1.81 kg	1.86 kg	Total
CO						
Number of piglets	2	139	780	706	49	1676
Percentage stillborn	50	10	8	4	4	6
Relative risk stillborn	7.25	1.45	1.16	0.58	0.58	0.87
OR						
Number of piglets	7	197	796	497	24	1521
Percentage stillborn	57	15	7	3	0	6
Relative risk stillborn	8.26	2.17	1.01	0.43	0	0.89
UC						
Number of piglets	4	121	684	539	40	1388
Percentage stillborn	50	19*	10	4	3	8*
Relative risk stillborn	7.25	2.75	1.45	0.58	0.43	1.18
Overall						
Number of piglets	13	457	2260	1742	113	4585
Percentage stillborn	54	15	8	3	3	7
Relative risk	7.83	2.17	1.16	0.43	0.43	1

*Chi-square analysis indicated that UC differs from control ($P < 0.05$).

uterine secretion of folate binding protein during early pregnancy does not correlate with folate binding protein mRNA (Vallet et al., 1998a, 1999a,b), making analysis of endometrial secretion of folate binding protein after implantation much more difficult. An overall understanding of folate transport in the pig is further confounded by the presence of a placental folate binding protein, which also has not been well characterized throughout pregnancy (Vallet et al., 1999b). How secreted folate binding protein and placental folate binding protein interact with each other to accomplish folate transport to the developing conceptus, as well as the identification of factors and mechanisms governing the production of each protein, requires further study.

Stillbirths

As previously indicated, fetal weights are negatively associated with uterine capacity but positively correlated with perinatal survival (Christianson, 1992). Our recent results confirm that lower piglet weight is associated with greater risk of stillbirths (Table 3). Interestingly, selection for uterine capacity for 11 generations may have increased the incidence of stillbirths in the line selected for uterine capacity. However, selection had no effect on either placental or fetal weights (Christenson and Leymaster, 2000). Thus, mechanisms of conceptus losses due to limitations in uterine capacity and losses due to stillbirth may oppose each other, and final litter size may be a balance between these factors. In contrast to pigs, in ruminants, difficulty during delivery has been shown to increase the risk of stillbirths, and difficulty in delivery in turn has been shown to be correlated with heavier offspring (Nix et al., 1998; Meyer et al., 2000). Thus, in all domestic species, an understanding of those aspects of uterine function that result in differences in offspring weight at birth could potentially alter the incidence of stillbirths and reduce perinatal losses.

Implications

Recent evidence suggests that embryonic mortality, uterine capacity, and stillbirths are influenced by conceptus size, and that this in turn is modulated by uterine function. Results suggest that both uterine function and conceptus development throughout pregnancy in domestic livestock can be manipulated by alterations in progesterone during the first few days after ovulation. The consequences of these changes in conceptus development require further study but potentially offer ways to influence embryonic, fetal, and neonatal survival of domestic livestock. The potential also exists for further alterations in conceptus survival by focusing specifically on uterine function that influences development of the fetal blood supply. Taken together, these results suggest that manipulation of uterine function is one avenue that could be used to decrease conceptus losses during pregnancy in all livestock species.

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